Influenza pandemic risk factors associated with solar cycle extremes, low solar and geomagnetic activity, cold-glacial climate change and geographic origination (1500-2018).

Short title: Influenza pandemic risk factors associated with solar activity and cold climate change.

Author information

Carlton B. Brown[1]¶ *

1 Affiliations: Veterinarian, private researcher and author, Raglan, Waikato, New Zealand.

*Corresponding author

Email: carlton@grandsolarminimum.com (CBB)

Word count:

Abstract: 300

Manuscript: 11,047 (excluding abstract, references and supporting information captions)

Key words: influenza; pandemic; epizootic; zoonosis; risk factor; circadian system; cold stress; immunosuppression; infectious aerosols, solar activity; geomagnetism; cosmic rays; climate change.

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Abstract

There is no means of predicting when influenza pandemics could occur. This exploratory study addressed a crucial knowledge gap in influenza pandemic risk factor understanding associated with solar and geomagnetic activity, cold-glacial climate change and geographic origination. Influenza pandemics, regional epidemics, concurrent epizootics and geographic details were compiled from expert reviews. Risk factor assessment utilized numerous statistical methods and 10 multi-century solar activity and climate change variables. Sixteen polar ice cores were used to benchmark the study period climate relative to the peak Holocene Climate Optimum temperature 8 kiloyears ago. There was a grand mean 0.92 pandemics (SE=0.15) per 11-year sunspot number cycle since 1700 (n=25). Logistic regression demonstrated a higher pandemic probability at sunspot number peaks (P01) and troughs (T01) +/-1-year compared with other cycle stages (P01: P=0.01, Odds ratio OR=4.2. T01: P=0.03, OR=3.4). Multiple logistic regression confirmed SSN P01+T01 stages and positive cosmic ray intensity anomalies relative to its 1961-1990-reference period mean (RPM) as pandemic and epidemic predictors-triggers respectively ($Pr>|z|<0.05$, 1700-). Simple logistic[1] and linear[2] regression identified increased cosmic ray intensity, Beryllium10 radionuclide, Arctic sea ice cover, Greenland ice accumulation rate, colder Greenland and Northern Hemisphere temperatures, and lower sunspot numbers and total solar irradiance relative to their RPM as outbreak[1] and annual outbreak rate[2] predictors ($P<0.05$, 1-11yr moving average[1] and cycle mean[2] anomalies, 1500-[1], 1700-[1,2]). By mid-study Greenland was at its coldest post-Holocene Climate Optimum temperature in 8-kiloyears (mean -4.8°C, n=10 ice cores), or -21% of its prior Holocene interglacial increase (mean +23.3°C). Four categories of outbreak risk factors putatively implicating “immunological susceptibility and induced immunosuppression” were identified. These included 11-year solar cycle extremes, low solar and geomagnetic activity, Arctic cold and glaciation (*linked to glacial cycle stage*) and geographic risk (*Europe, North America, Russia, China*).

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Introduction

The Little Ice Age (mid-13th to mid-19th centuries) was the coldest period after the Holocene Climate Optimum (HCO, peak glacial cycle temperature), which coincided with five millennia of neoglacial advances that peaked in size mid-study [1], [2]. This period was hallmarked by regional catastrophes associated with cold-glacial climate change, including famine, wars, and epidemics [3], [4]. Dozens of influenza pandemics and regional epidemics, and other diseases, occurred during this period. Pandemics could infect 30-50% of the population within 1-2 years, and were associated with explosive disease spread, and varying mortality rates and geographic extents [5]–[11]. Some 20th-21st century influenza pandemic mortality rates were estimated at 1–3% (1918), 0.03% (1968), and 0.001–0.007% (2009) [12].

There is no means of predicting when influenza pandemics could occur because the risk factors associated with pandemics are not well understood [13]. Therefore, to better prepare for future pandemics (H5N1, H7N9 etc.) we must explore if the spate of zoonoses and pandemic since 1997 were the result of unknown mitigable risk factors. Three categories of risk factors putatively-thematically implicating "immunological susceptibility and induced immunosuppression," and one linked to the study period's stage of the glacial cycle were evident in the literature.

Firstly, *timing risk* has been linked to the extremes of the 11-year sunspot number (SSN) cycle (see Hope-Simpson paragraph). Sunspots represent dark patches of intense magnetic fields that loop through the surface of the sun [14]. An 11-year SSN peak and trough concentration of outbreaks potentially implicates changes in solar magnetic polarity [15] or heliospheric magnetic flux [16], [17]. Theoretically, circadian system cryptochrome repressor proteins whose photoreduction spin chemistry is magnetoreceptive (a *radical-pair mechanism*), interacting with circadian core molecular clockwork, could offer a means by which solar-/geo-magnetism modulated immuno-inflammatory biology [18]–[20]. The circadian system core molecular clockwork controls the immune and inflammatory systems via oscillatory transcriptional activators (CLOCK–BMAL1) and repressors (Cryptochrome1/2, Period1/2) [21]. Coincidentally, the influenza-A virus (IAV) evolutionarily linked its replication cycle to the

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69 circadian system (time of day, winter) [22], [23]. Thus, solar cycle extremes could have dysregulated
70 immune responses, [24], [25] to aid viral entry and replication in immunologically susceptible animals
71 (epizootics), people (zoonosis, family clusters), and populations (epidemics, pandemics).

72 Secondly, *geographic risk* reflects the prior cited expert reviews [5]–[11]. Geographic risk considers the
73 role of innate immunity single nucleotide polymorphisms (SNPs) in creating immunological susceptibility
74 in people of certain ethnicities (Caucasian, Chinese) to novel-zoonotic IAV infection [26], [27], in regions
75 pertinent to outbreak origination (Europe, North America, Russia, and China). Increased cosmic rays and
76 ionizing radiation have been linked to *immunosuppression* and increased infectious disease mortality
77 [28]–[30]. Peak levels of cosmic ray induced ionization occurred during the Maunder minimum (mid-
78 study) associated with latitudinal and magnetic dipole variations, implicating northern European latitudes
79 and the Far East [31]. Regional-scale immunosuppression could implicate increased cosmic rays directly
80 and indirectly via its climate change impact linked to solar-/geo-magnetism (low cloud cover) [32].
81 Equine and migrating-avian viral reservoirs and ecology must also be considered in geographic risks.

82 The literature is devoid of quantitative pandemic risk factor studies associated with solar activity and/or
83 climate change spanning the study period (1500-), beyond timing risk studies (1700-). Therefore thirdly,
84 *climate change risks* reflect shorter-term cold weather influences on seasonal influenza and avian
85 influenza epizootics. Firstly, the degree and duration of *cold stress* dysregulate immune responses [33],
86 [34], implicating key immuno-molecular pathways coopted by IAVs during infection (e.g. Nuclear Factor
87 kappa B, NF-κB) [35], [36]. Secondly, cold weather modulates the formation and dispersion of *infectious*
88 *aerosols*, their respiratory tract (RT) penetration, and drying out RT mucosa [37]. Thus, low temperature
89 and relative humidity were inversely correlated with influenza disease burden during cooler-drier winters
90 in temperate regions [38], [39]. A fourth risk factor linked to the mid-study period's stage of the glacial
91 cycle (coldest iciest post-Holocene Climate Optimum period) was evident in the literature (Discussion).

92 In 1978 Hope-Simpson published a Nature correspondence suggesting 20th century pandemics were
93 associated with sunspot number maxima [40]. A few statistical studies since reported pandemic timing

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risk associated with the 11-year international sunspot number cycle peaks +/- 1-year (Tapping) [41], and troughs +/- 1-year as well (Ertel, Qu) [42], [43], or sunspot numbers exceeding percentile thresholds (Yeung) [44]. This sunspot cycle timing risk was also demonstrated with SARS-CoV-2 (2019 sunspot number trough) and is claimed for Ebola [45]. Pandemics have also been linked with grand solar minimum periods [46], [47].

Towers, an expert biostatistician, falsified the Tapping, Ertel, and Yeung studies after applying more robust statistical methodologies to their corrected outbreak lists [48]. Qu more recently used Yeung's pandemic list and logistic regression analysis to show that sunspot number maxima and minima +/– 1-year were risk factors. The influenza outbreak consensus lists used by Tapping, Ertel, and Yeung (also Qu) were derived from numerous publications (1927-1998, median 1986). These publications detailed different geographies over different periods using varying pandemic definitions and data sources, which likely resulted in incompleteness, inaccuracy, and uncertainty [5], [6]. Solar-pandemic timing risk study lists either utilized the historian lists as provided (Tapping) or criteria to derive smaller consensus lists (Ertel, Yeung, Qu), meaning valuable outbreak data was discarded. No previous solar activity-pandemic outbreak lists detailed regional epidemics, concurrent epizootics, or geographic origin and extent.

Comprehending the high-level chain of biological events common to all novel-zoonotic IAV infections, irrespective of whether that IAV arose by mutation, recombination, or reassortment [49], aids an immunology orientation to this study. Geographically expansive outbreaks arose when a novel-zoonotic IAV emerged for which a susceptible population (broad demographics) lacked pre-existing protective immunity (neutralizing antibody and/or cellular immunity). At the same time, all novel-zoonotic IAVs overcame and/or dysregulated immunological defenses (innate and early adaptive immunity), physical (mucosal surfaces), and cellular barriers (cell attachment and entry, intracellular restriction factors) [50]–[52]. The IAV then replicated in the respiratory tract in sufficiently high titers and was transmitted to a second person. This biological journey will be referred to as "Bottleneck-1", and only after this was surmounted could geographically expansive transmission have occurred ("Bottleneck-2") [53].

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Influenza pandemics, regional epidemics, concurrent epizootics and their geographic details were compiled from seven expert reviews, and organized into five category groupings. Outbreaks were (re)classified according to WHO Phase 5 and 6 pandemic descriptions based on pooled geographic information. Numerous regression and other statistical methods were used to define risk factors, probabilities, and predictors from among 10 solar-/geo-magnetic activity (*proxied by cosmic ray intensity, 10-Beryllium cosmogenic radionuclide, solar modulation function, sunspot numbers*) and solar electromagnetic activity (*proxied by total solar irradiance*), and climate change variables (*proxied by Northern Hemisphere and Greenland temperatures, Artic sea ice cover, Greenland ice accumulation rate*) spanning 3-5 centuries. All data was geographically relevant to outbreak origination and dissemination and animal-IAV reservoirs. Sixteen polar ice cores were used to benchmark the study period's climate relative to the Holocene Climate Optimum peak glacial cycle temperature 8kyr ago.

Materials and methods

A detailed description of database and analytical methods, links to the publicly available data used in this study, description-preparation of the solar-/geo-magnetic and climate change data, data and results quality assurance and control, and the R code and R output .txt files are available online (readme notes, Figshare).

Pandemic and epidemic database

Influenza pandemics, regional epidemics and concurrent animal epizootics from 1500-2009 were identified in seven reviews (2001, 2008-2011) by six expert professors [5]–[11]. Key information was summarized from these reviews and 32 pooled review-cited sources, and tabulated into categories defined in S1 Fig. A pandemic reflected an expert-reviewer's explicitly stated description of an 'influenza' outbreak, which was confirmed in the pooled literature in ≥2 WHO regions, whereas an epidemic reflected expert descriptions of an 'influenza' outbreak confirmed in one WHO region (≥2 countries, or stated as regional). This classification was consistent with WHO Phase 5 regional epidemic and Phase 6 pandemic descriptions [54], thus enabling an objective (re)classification of outbreaks based on pooled

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geographical information. This method avoided subjective disease severity judgments based on incomplete information, while reflecting that not all outbreaks resulted in severe disease with high mortality that left their mark in the global historical record, especially pre-1700.

Pandemic and major regional epidemic ("epidemic") data was pooled for combined and separate analysis, and robustness testing, as follows:

1) Category A pandemics (pandemics +/-epizootics/zoonosis plus epidemics with epizootics/zoonosis) (epizootic/zoonosis = epizoo, category = Cat.),
2) Cat.B epidemics (epidemics without epizootics/zoonosis),
3) Pandemics +/-epizootics (pandemics +/-epizootics/zoonosis),
4) Epidemics +/-epizootics (epidemics +/-epizootics/zoonosis).

Solar activity and climate change data

Annually resolved datasets starting between 1500 and 1700 and ending post-1994, were obtained from the National Oceanic and Atmosphere Administration (NOAA), Laboratory for Atmospheric & Space Physics Interactive Solar Irradiance Data Center, and WDC-SILSO Royal Observatory of Belgium websites. The following datasets were collected for analysis and benchmarking:

Solar-/geo-magnetic activity related datasets: international sunspot numbers (SSN data) [55], and group sunspot numbers (GSSN data) [56], cosmic ray intensity (CRI data) [57], solar modulation function (MeV data) [58], 10-Beryllium radionuclide (^{10}Be data, see missing data comment in the readme file, Figshare) [59]. Geomagnetic activity index data was also downloaded for correlation analysis (GMA-AA data, 1868-) [60], given solar modulated geomagnetism (solar-/geo-magnetism) controls atmospheric cosmic ray entry and ionization [61]. *Solar electromagnetic activity dataset:* total solar irradiance (TSI data) [62].

Climate change datasets: Northern Hemisphere temperature (NHT°C data) [63], Greenland ice core derived temperature (GT°C data) [64], Arctic algal growth anomaly (inverse sea ice cover proxy, SIC data) [65], and Greenland ice accumulation rate (IAR data, see ^{10}Be missing data comment above, same

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dataset) [59]. All terrestrial-derived datasets were geographically relevant to influenza outbreaks and animal-IAV reservoirs.

Data was provided as, or converted to *anomaly data* relative to the climate reference period mean (RPM), generally the 1961-1990 mean (except SIC and MeV), per the norms of the scientific community for long-term climate change assessments [66]. A negative NHT°C and GT°C anomaly indicated a colder temperature than the 1961-1990 RPM. A negative SIC anomaly indicated less crustal algal growth than at its RPM due to less sunlight reaching the sea floor rocks, corresponding with an increase in sea ice cover [65]. A positive IAR indicated increased Greenland glaciation rates above the RPM. A negative SSN, GSSN, TSI, and MeV anomaly, and a positive CRI and ^{10}Be indicated solar activity lower than the RPM.

A glacial cycle perspective on outbreak risks was obtained by benchmarking the 11,400-year GT°C dataset against 15 other Polar ice cores, utilizing two-three immutable glacial cycle landmarks. For *analytical and graphical purposes*, the glacial cycle peak temperature closest to the end of the prolonged interglacial rise was termed the Holocene Climate Optimum (HCO); the Little Ice Age (LIA) temperature nadir corresponded with the lowest post-HCO temperature trough during the LIA period (mid-13th-19th centuries). The lowest temperature trough of the last glacial cycle immediately prior to the sustained interglacial temperature rise was termed the Last Glacial Maximum (LGM). The Holocene interglacial was the period between the LGM and HCO. *Benchmarking datasets*: Greenland; (Vinther data) [67], (Alley data) [68], (Buizert, nine different Greenland ice core locations) [69]. Antarctica; (Jouzel data, EPICA Dome C) [70], (Uemura data, Dome Fuji) [71], (Lorius data, Vostok) [72], (Mulvaney data, James Ross Island) [73].

Basic data analysis

Basic statistical parameters were assessed for each independent variable (IV: number of years, mean, median, minimum, maximum, standard deviation-SD, confidence intervals). The normality of data distribution was assessed by skewness (within +/-2), and kurtosis (within +/-7) values because all datasets

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exceeded 300 years [74]. Eleven correlation matrices (1–11-year SMA periods) were produced between ten solar-/geomagnetic and electromagnetic activity and climate change variables (SSN, 10Be, CRI, MeV, TSI, GMA-AA, and NHT°C, GT°C, SIC, IAR). Collinearity was assessed during multiple logistic regression analysis using the variance inflation factor (VIF). For this study, a VIF>10 was considered problematic, a VIF>5 was highly correlated, and a VIF>2.5 was moderately correlated [75].

Outbreak distribution by solar cycle stage (timing risk factors)

Influenza outbreak distributions across the 11-year solar cycle since 1700 were investigated (Fig 1A) using simple logistic regression. This method was used to derive the probability of an outbreak by solar cycle stage groupings, for SSN, GSSN, and TSI cycles [76]. Investigatory stage groupings comprised the peak +/- 1-year (P01), trough +/- 1-year (T01), and the combined peak and trough +/- 1-year (P01+T01), versus the combined inter-peak-to-trough plus inter-trough-to-peak stages (P_T+T_P) (Fig 1B).

Fig 1: International sunspot number cycles and influenza outbreaks since 1700. (A) Sunspot numbers from 1700-2018 depict solar cycles with varying periodicities, including the 11-year Schwabe cycle and other superimposed longer-term "grand solar" cycles that modulated the magnitude of the 11-year Schwabe cycle SSN peaks and troughs. During the Little Ice Age and study period, there were numerous grand solar minimum periods, including the Wolf (1270-1340), Spörer (1390-1550), Maunder (1640-1720), Dalton (1790-1830), and Gleissberg–Gnevishev (1898–1923) minima [77]–[79]. Since the 1957 Solar Cycle-19 SSN peak, all Schwabe cycle peaks have declined, indicating the sun entered a new grand solar minimum period. **(B)** An extracted Schwabe cycle (1843-1856) is used to demonstrate the solar cycle stage classification used to create binary variables for regression analysis. Data citations: Outbreak database expert reviews [5]–[11]. Sunspot number data [55].

Logistic regressions were estimated according to the following equations:

$$ln\left(\frac{p}{1-p}\right) = b_0 + b_1 \cdot D_{P01} + b_2 \cdot D_{T01} \text{ (for P01and T01 separately).} \quad (1)$$

Where D_{P01} is a dummy variable: 1 for P01, and 0 for all other cycle stages; D_{T01} is a dummy variable: 1

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for T01, and 0 for all other cycle stage; b_1 and b_2 are regression coefficients.

$$ln\left(\frac{p}{1-p}\right) = b_0 + b_1 \cdot D_{P01T01} \text{ (for the combined P01+T01)} \quad (2)$$

Where D_{P01T01} is a dummy variable (0 for P_T+T_P, and 1 for T01 and P01); b_0 is the intercept, b_1 is the dummy variable coefficient. These formulas were used to determine the coefficients b_1 or b_1 and b_2, enabling the determination of the effect of the stage grouping on outbreak probability (increase, decrease, no impact). Cycle stage probabilities and Odds ratios (OR) were then derived.

The Fisher's exact test of independence was used to assess differences in solar cycle stage distributions between pandemic +/-epizootics versus epidemic +/-epizootics, for cycles defined by SSN, GSSN, TSI, CRI, and MeV periodicities. This method compared the differences in the proportion of years with an influenza outbreak over key stages of the solar cycle post-1700. Stage comparisons included P01, T01, and P01+T01 versus T_P+P_T, and P+T, and P+T (exact peak plus trough) versus All stages-(P+T). The outbreak proportion was calculated as the number of years with outbreaks multiplied by 100 and divided by the total stage years.

Logistic and linear regression analysis (non-timing risk factors)

Three regression methods were utilized to identify non-timing outbreak risk factors, and understand what factors increased or decreased the probability of an outbreak. Firstly, a simple logistic regression was used to investigate the impact of a single independent variable (IV) or predictor in explaining the variability of the dependent variable (outbreak category), in case the outcome was binary [80] [81]. Logistic regressions were estimated according to the following equation [82]:

$$In\left(\frac{p}{1-p}\right) = b_0 + b \cdot X_i \quad (3)$$

Where p was the probability that an outbreak existed in a certain year; Xi is one of the IVs (SSN, GSSN, TSI, CRI, MeV, 10Be, NHT°C, GT°C, SIC, and IAR); ln (Ln) denotes the natural logarithm; b_0 and b are

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regression coefficients. Ten logistic regressions based on model (3) were estimated using the raw anomaly and a 2–11-year SMA data (one-sided moving average) from 1500- and 1700-. Data smoothing was used to determine if the predictive utility was improved by removing short-term volatility, and to reflect the sequential increase in Pearson correlation coefficients between 2 and 11 years with solar-/geo-magnetic activity and electromagnetic activity variables, versus climate change variables.

Secondly, it was investigated if the mean number of outbreaks per solar cycle year could be predicted by the cycle mean anomaly, where cycle timelines were defined by SSN, GSSN, TSI, CRI, and MeV trough-to-trough periods (T_T, from 1700-). Simple linear regression was used to check for linear associations between these continuous variables [83]. For each set of cycles defined by SSN, GSSN, TSI, CRI, and MeV, 10 linear regressions were estimated according to the following equation [80]:

$$Y'_i = a_0 + a \cdot \overline{X_i} \qquad (4)$$

Where Y'_i was the predicted mean number of category outbreaks per year for cycle number i, $\bar{X}_i$ is an average of the independent variable (one of SSN, GSSN, TSI, CRI, MeV, ^{10}Be, NHT°C, GT°C, SIC, and IAR) for cycle i, a_0 and a are corresponding regression coefficients.

Thirdly, multiple logistic regression was conducted to investigate the simultaneous impact of up to eight IV predictors (assessed 1–11-year SMA) plus a SSN P01+T01 dummy variable on the probability of five different categories of influenza outbreaks. A stepwise (SW) backward method was used and 55 models were assessed based on mathematical criteria. An initial multiple logistic regression equation contained all IVs as follows (from 1700-) [84] [85]:

$$\ln\left(\frac{p}{1-p}\right) = b_0 + b_1 \cdot \mathrm{Dummy_{SSN}} + b_2 \cdot \mathrm{TSI} + b_3 \cdot \mathrm{CRI} + b_4 \cdot \mathrm{MeV} + b_5 \cdot \mathrm{Be10} + b_6 \cdot \mathrm{NHT°C} + b_7 \cdot \mathrm{GT°C} + b_8 \cdot \mathrm{SIC} + b_9 \cdot \mathrm{IAR} \qquad (5)$$

Where p is the probability an event existed in a particular year; ln denotes the natural logarithm; b_0 and $b_{1\text{-}9}$ are regression coefficients. Predictors were then iteratively removed, and an interim

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assessment made using the Akaike information criterion (AIC). This was continued until the most reduced model was identified comprising the lowest AIC value, with at least one significant variable (Pr>|z|<0.050) plus associated marginal predictors (Pr>|z|<0.20, but mainly Pr>|z|<0.15).

Outbreak distribution by variable anomaly quartile groupings

Chi-squared and Fisher's exact tests of independence were used to assess anomaly magnitude and sign quartile grouping proportion differences in outbreaks (1500-, 1700-). Independent variable anomalies were classified into six categories based on percentiles: large, medium, and small negative and positive quartiles. An anomaly below the 25th percentile was considered “low,” above the 75th percentile “large,” and between 25th and 75th percentiles “medium” for both positive and negative anomalies. For each outbreak category, the number of years with and without outbreaks was calculated, from which quartile grouping proportions were calculable in R. Chi-squared (used when the expected frequency ≥5) and Fisher's exact tests (used when the expected frequency <5) of independence were used to compare differences between the observed frequency (fo) and expected frequency (fe) distributions of outbreaks (proportions) by quartile groupings [86].

General statistical analysis considerations

This exploratory study involved the use of multiple statistical analyses each with implicit sub-hypotheses using continuous data and fixed outbreaks, without any form of random sampling procedure. No P-value corrections were made for multiple comparisons to ensure the risk of rejecting important discoveries was minimized, given the catastrophic nature of pandemics and the exploratory-ground breaking scope of this study. Subsequent smaller-scale confirmatory studies with preplanned hypotheses should be conducted to confirm the observed associations [87], [88]. Statistical analyses were conducted using R statistical programming language (version 4.0.2) and Microsoft Excel (Mac). For exploratory science purposes, a 2-sided P-value <0.05 or Pr(>|z-score|) <0.05 was considered statistically “significant.”

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Results

Influenza outbreak database overview

The outbreak database details 49 regionally expansive influenza outbreaks identified within the seven expert reviews, which confirmed geographic extent (n = 49/49), origination (n = 49/49), and concurrent epizootics/zoonosis (n = 21/49). Text confirmation of geographic extent, and other relevant information, was provided by a median of 3.0 expert reviews (range = 1-7, mean = 3.2,) and median of 5.0 review-cited publications (range = 1-9, mean = 4.7) per outbreak. Three outbreaks were removed from the provisional pooled list (n = 52) because geographic extent was unverifiable (1529, 1793, and 1843). No new outbreaks from outside the seven reviews were added. Database summary results are provided in S1 Table. The 49 outbreaks were split into 31 pandemics comprising 15 concurrent epizootics (48%), and 18 regional epidemics comprising 6 concurrent epizootics (33%, Fig 2A). Epizootic frequencies were not significantly different between outbreak categories (Chi-square: X^2 = 1.1, p = 0.30, df = 1). Equine epizootics accounted for 76% (n = 16/21) of all concurrent influenza epizootics (Fig 2B).

Fig 2. Influenza pandemic and regional epidemic outbreaks between 1500 and 2018. (A) Database summary of the influenza pandemic and major regional epidemics +/-concurrent epizootics/zoonosis, and Cat.A&B outbreaks, from 1500- and 1700- to 2018. **(B)** Summarizes the total number of pandemics and major regional epidemics (1500-2018), and the number and percentage of outbreaks associated with concurrent epizootics/zoonosis (zoonosis proxy). This summary information was derived from the S1 Table. Outbreak database expert reviews [5]–[11].

Geographic origination was confirmed for 49 of 49 outbreaks, either emphatically (n = 45) or ambivalently (n = 4, Europe or Nth. America?). Where geographic origination was specified, it was concentrated in Europe (EUR n = 21, including Russia n = 5), the Americas (AMR, primarily North America, n = 15), and Asia (n = 8 WPR and SEAR, incl. China n = 4 since 1830) (Fig 3).

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306

307 **Fig 3. The geographic origination of influenza outbreaks +/-concurrent epizootics/zoonosis.** Summary of the
308 influenza outbreak database detailing the geographic origin of pandemics and major regional epidemics +/-
309 concurrent epizootics/zoonosis between 1500 and 2018. This summary information was derived from the S1 Table.
310 Outbreak database expert reviews [5]–[11].

311 All influenza pandemics from the 1918 Spanish flu, including 1946, 1957, 1968, 1977, and 2009
312 pandemics, the 1976 swine flu epidemic (USA zoonosis, confirmed human-to-human transmission), as
313 well as the first avian H5N1 (1997) and H7N9 (2013) zoonosis, all occurred within one year of the SSN
314 peak or trough. This SSN peak and trough association was shared by 76% of all outbreaks since 1700 (n =
315 26/34). Forty-one to 44% of outbreak categories comprising pandemics occurred at the SSN peak +/-1-
316 year and 35-36% at the SSN trough +/-1-year.

317 Simple logistic regression analysis demonstrated the probability of a pandemic was significantly higher
318 within P01, T01, and P01+T01 stages than P_T+T_P stages of the 11-year solar cycle (n = 24/27
319 comparisons $P<0.050$, n = 2/27 with P = 0.051 and 0.056, and n = 1/27 with P = 0.08 for cycles defined
320 by SSN, GSSN, and TSI periodicities). These probabilities translated into a mean Odds ratio (OR) of 2.9
321 (T01), 3.3 (P01), and 3.1 (P01+T01) compared with the P_T+T_P, averaged across all SSN, GSSN, and
322 TSI cycles and categories comprising pandemics, or a mean OR = 3.1 for all SSN, GSSN, TSI, stages and
323 categories comprising pandemics. The S2 Table contains a summary of the beta coefficients, P-values,
324 stage probabilities (p), and Odds ratios (OR) and 95% confidence intervals. The Fig 4 summary
325 information was derived from S2-S4 Tables.

326

327 **Fig 4. Solar cycle stage grouping outbreak probabilities and Odds ratios. (A)** Odds ratios for P01 (peak +/-1
328 year), T01 (trough +/-1 year), and combined P01+T01, compared with the inter-peak-trough plus inter-trough-peak

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stages (P_T+T_P), for solar cycles defined by SSN, GSSN, and TSI T_T periodicities, for different categories of pandemics (Cat. A&B, Cat. A, and pandemics +/-concurrent epizootics/zoonosis). The Asterix above each P01, T01, and P01+T01 Odds ratio bar indicates a significant difference over P_T+T_P stage probabilities ($p<0.050$). This data was derived from the S2 Table, which in turn was derived from S3 Table. **(B)** The number of influenza outbreaks by SSN cycle stage groupings for different categories of influenza outbreaks and the number of years in each stage grouping (far right bar). These results were derived from the S4 Tables. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55], [56], [62].

The Fisher's exact test results showed there were no significant differences in solar cycle stage frequency distributions between pandemics and epidemics +/-epizootic (all $P \geq 0.20$, except one $P = 0.12$, S5 Table).

Simple logistic regression analysis revealed non-timing risks factors

There was a higher probability of an outbreak during sustained (1-11yr SMA) cooling (-GT°C, -NHT°C anomalies) and glaciation periods (-SIC crustal algal growth = increased sea ice cover, +IAR anomalies), relative to their respective RPM. Significant negative regression coefficients were obtained between GT°C and Cat.A&B outbreaks (all B = -0.6, all $P<0.04$, n = 48, 1–11-year SMA, 1500-), and with NHT°C and epidemics +/-epizootic since 1500 (all B = -2.8 to -3.1, all P = 0.01, n = 18, 1–11-year SMA) and 1700 (all B = -3.4 to -3.6, all P = 0.01, n = 9, 1–11-year SMA). A significant negative coefficient indicates a reduced outbreak probability as the GT°C and/or NHT°C increased above the RPM, and vice versa. Results in this section refer to Table 1 and S6 Table.

Table 1. Coefficients of simple logistic regression and P-values by outbreak category

Outbreak	**A&B**	**Epi***	**Epi***	**Epi***	**Epi***	**Epi***	**A&B**	**A**	**Pan***	**Epi***	**A&B**	**Epi***	**Epi***	**Epi***	**Epi***	**Epi***	**Epi***	**Pan***	**Epi***	**Pan***
Start Year	**1500**	**1500**	**1700**	**1610**	**1700**	**1700**	**1700**	**1700**	**1700**	**1500**	**1700**	**1700**	**1700**	**1700**	**1610**	**1500**	**1700**	**1610**	**1500**	**1500**
Variable	**GT°C**	**NHT°**	**NHT°**	**TSI**	**CRI**	**MeV**	**SIC**	**SIC**	**SIC**	**IAR**	**CRI**	**TSI**	**SSN**	**GSSN**	**GSSN**	**Be10**	**Be10**	**TSI**	**MeV**	**MeV**
Raw Data	-0.6	-2.8	-3.4	-1.6	6.1	-0.01	-0.9	-0.9	-0.8	12.5					-0.3			0.8		0.002
	(0.04)	(0.01)	(0.01)	(0.02)	(0.002)	(0.02)	(0.01)	(0.02)	(0.04)	(0.04)					(0.04)			(0.048)		(0.02)
2yr SMA	-0.6	-2.9	-3.4	-1.4	6.5	-0.01	*-0.8*													0.001
	(0.04)	(0.01)	(0.01)	(0.03)	(0.001)	(0.02)	*(0.052)*													(0.04)
3yr SMA	-0.6	-2.9	-3.4	-1.4	6.6	-0.01					1.8					1.1	1.6			
	(0.04)	(0.01)	(0.01)	(0.04)	(0.001)	(0.02)					(0.04)					(0.04)	(0.03)			
4yr SMA	-0.6	-2.9	-3.4	-1.4	6.6	-0.01	-1.0				2.0	-2.5								
	(0.03)	(0.01)	(0.01)	(0.04)	(0.001)	(0.02)	(0.04)				(0.02)	(0.05)								

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5yr SMA	-0.6	-3.0	-3.5	-1.4	6.7	-0.01	-1.0				2.2	-2.7	-0.02	-0.4	-0.3					
	(0.03)	(0.01)	(0.01)	(0.04)	(0.000)	(0.02)	(0.03)				(0.01)	(0.04)	(0.047	(0.04)	(0.049					
6yr SMA	-0.6	-3.0	-3.5	-1.5	6.7	-0.01	-1.1			41.3	2.3	-2.9	-0.03	-0.5	-0.3		*1.7*			
	(0.03)	(0.01)	(0.01)	(0.03)	(0.000)	(0.01)	(0.03)			(0.02)	(0.01)	(0.03)	(0.02)	(0.02)	(0.03)		*(0.051)*			
7yr SMA	-0.6	-3.0	-3.5	-1.5	6.5	-0.01	-1.0				2.3	-3.2	-0.03	-0.5	-0.3					
	(0.03)	(0.01)	(0.01)	(0.03)	(0.000)	(0.01)	(0.047)				(0.01)	(0.02)	(0.01)	(0.02)	(0.04)					
8yr SMA	-0.6	-3.0	-3.5	-1.6	6.5	-0.01	*-1.0*				2.3	-3.4	-0.04	-0.6	-0.3					
	(0.04)	(0.01)	(0.01)	(0.02)	(0.000)	(0.01)	*(0.054)*				(0.02)	(0.02)	(0.01)	(0.02)	(0.03)					
9yr SMA	-0.6	-3.0	-3.5	-1.6	6.6	-0.01					2.2	-3.5	-0.04	-0.6	-0.4					
	(0.04)	(0.01)	(0.01)	(0.03)	(0.000)	(0.01)					(0.02)	(0.02)	(0.01)	(0.01)	(0.01)					
10yr SMA	-0.6	-3.1	-3.5	-1.6	5.9	-0.01						-3.8	-0.04	-0.7	-0.5				-0.003	
	(0.04)	(0.01)	(0.01)	(0.03)	(0.002)	(0.01)						(0.01)	(0.01)	(0.01)	(0.01)				(0.049)	
11yr SMA	-0.6	-3.1	-3.6	-1.6	6.2	-0.01						-3.9	-0.04	-0.7	-0.5				-0.003	
	(0.04)	(0.01)	(0.01)	(0.02)	(0.001)	(0.005						(0.01)	(0.01)	(0.01)	(0.01)				(0.049)	
Years (n)	494	501	301	409	308	302	311	311	311	481	308	319	319	316	406	481	286	409	502	502
Outbreaks (n)	48	18	9	15	9	9	34	28	25	18	33	9	9	9	15	18	9	28	18	30

Coefficients of simple logistic regression and P-values (bracketed, below) for an array of solar activity and climate change variables (raw data, 2–11-year SMA), and different categories of influenza outbreaks between 1500- or 1700- and up to 2018. This summary results table was derived from R results in S6 Table. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

The Arctic crustal algal growth anomaly (sea ice cover proxy, SIC) raw data yielded significant negative regression coefficients for all categories comprising pandemics since 1700 (all B = -0.8 to -0.9, all P = 0.01-0.04, Cat.A&B n = 34, Cat.A n = 28, pandemic +/-epizootic n = 25), and with Cat.A&B outbreaks and SIC 4–7-year SMA anomalies (all B = -1.0 to -1.1, all P = 0.03-0.047, n = 34). A negative coefficient indicates a reduced outbreak probability as the SIC crustal algal growth increased above the RPM (meaning less sea ice), and vice versa. A significant positive regression coefficient was obtained with the ice accumulation rate (IAR) anomaly and epidemics +/-epizoo since 1500 (B = 12.5 and 41.3, P = 0.04 and 0.02, n = 18, raw data and 6-year SMA). A positive coefficient indicates an increased outbreak probability as the IAR increased above the RPM (Greenland glacier growth), and vice versa.

There was a higher probability of an outbreak during periods of low solar activity. Significant negative regression coefficients were obtained with epidemics +/-epizoo and TSI since 1610 (all B = -1.4 to -1.6, all P = 0.02-0.04, 1–11-year SMA, n = 15) and 1700 (B = -2.5 to -3.9, P = 0.01-0.05, 4–11-year SMA). Significant negative regression coefficients were also obtained between epidemics +/-epizoo and SSN (all

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B = -0.02 to -0.04, all P = 0.01-0.047, 5–11-year SMA, n = 9, 1700-), and with GSSN since 1610 (all B = -0.3 to -0.5, all P = 0.01-0.049, 1-year and 5–11-year SMA, n = 15) and 1700 (all B = -0.4 to -0.7, all P = 0.01-0.04, 5-11 year SMA, n = 9). Negative coefficients indicate a decreasing outbreak probability as the TSI, SSN, and GSSN increased above the RPM, and vice versa. The P-value significance level increased with data smoothing for these solar activity-cycle variables (from 5 to 11yr SMA).

Significant positive regression coefficients were yielded between CRI and Cat.A&B (all B = 1.8-2.3, all P = 0.01-0.04, 3–9-year SMA, n = 33) and epidemics +/-epizootics (all B = 5.9-6.7, all P<0.01, 1–11-year SMA, n = 9) since 1700. Significant positive regression coefficients were also obtained for ^{10}Be and epidemics +/-epizoo since 1500 (B = 1.1, P = 0.04, 3-year SMA, n = 18) and 1700 (B = 1.6, P = 0.03, n = 9, 3-year SMA). A positive coefficient indicated an increasing outbreak probability as the CRI and ^{10}Be increased above the RPM (low solar-/geo-magnetic activity), and vice versa.

Simple linear regression analysis confirmed outbreak risk factors

There was a grand mean 0.08-0.11 outbreaks per solar cycle year across all influenza outbreak categories comprising pandemics (SE = 0.01-0.02 years or approximately 16% of their respective means, 1711-2008). This equated to a mean outbreak interval of 9 years (Cat.A&B), 10.7 years (Cat.A) and 12.1 years (pandemics +/-epizoo), or 1.2, 1.0, and 0.9 outbreaks respectively per mean 11-year solar cycle defined by SSN, GSSN, and TSI T_T periods (Figs 5A and B). Data is detailed in S7 Table.

Fig 5. The mean number of influenza pandemics per year and solar cycle duration. (A) The mean number of influenza pandemics (different categories) per solar cycle year since 1700 for SSN, GSSN, and TSI cycle T_T periods, with standard error bars (mean of means). The reciprocal of the yearly outbreak rate was the mean interval between outbreaks (detailed in the legend, right of graphic). **(B)** The mean solar cycle duration since 1700 derived from SSN, GSSN, TSI, CRI, and MeV trough-trough periods (years), with standard deviation bars. These graphics were derived from S7 Table. Data citations: Outbreak database expert reviews [5]–[11]. Solar activity cycle data

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used [55]–[58], [62].

Simple linear regression analysis confirmed the ability of cycle mean variable anomalies to predict the mean number of outbreaks per cycle year since 1700. Significant negative regression coefficients were obtained for cycle mean GT°C and mean Cat.A&B outbreaks per year (all B = -0.05 to -0.06, all P = 0.01-0.03, n = 26-27 SSN, GSSN, TSI, and CRI cycle T_T periods, or cycles), and mean pandemics +/-epizoo per cycle year (B = -0.04, P = 0.04, n = 27 TSI cycles). Significant negative regression coefficients were also yielded between mean cycle NHT°C and mean Cat.A&B outbreaks per year (B = -0.15 and -0.16 and P = 0.03 and 0.02, n = 27 and 26 TSI and CRI cycles respectively), and mean epidemics +/-epizootics per year (B = -0.10, P = 0.03, n = 27 TSI cycles). This indicates cycles (esp. CRI, TSI) with a mean GT°C and NHT°C anomaly greater than the RPM were associated with a lower pandemic and/or epidemic outbreak per cycle year probability, and vice versa. This section refers to Table 2 and S8 Table.

Table 2. Linear regression coefficients and P-values (mean cycle variable, mean outbreaks per cycle year).

Category	**A&B**	**Pan***	**A&B**	**Epi***	**A&B**	**A**	**Pan***	**Pan***	**Epi***	**Epi***	**A&B**	**Epi***	**Pan***	**Epi***
Independent	**GT°C**	**GT°C**	**NHT°C**	**NHT°C**	**SIC**	**SIC**	**SIC**	**IAR**	**IAR**	**Be10**	**CRI**	**CRI**	**MeV**	**TSI**
Solar cycle defined by:														
SSN (1711-2008, 27 T_T cycles)	-0.05				-0.11					0.07				
	(0.03)				(0.01)					(0.03)				
GSSN (1711-2008, 27 T_T cycles)	-0.06				-0.10					0.07				
	(0.01)				(0.01)					(0.03)				
TSI (1712-2008, 27 T_T cycles)	-0.05	-0.04	-0.15	-0.10	-0.11				-1.97	0.09				-0.09
	(0.03)	(0.04)	(0.03)	(0.03)	(0.01)				(0.04)	(0.02)				(0.05)
CRI (1721-2000, 26 T_T cycles)	-0.05		-0.16		-0.09	-0.08	-0.07				0.23	0.13		
	(0.02)		(0.02)		(0.01)	(0.03)	(0.04)				(0.03)	(0.01)		
MeV (1709-1997, 24 T_T cycles)								2.63					0.0002	
								(0.04)					(0.01)	

Coefficients of simple linear regression are summarized for an array of cycle mean independent variables and the cycle mean number of outbreaks per year for cycles defined by SSN, GSSN, TSI, CRI, and MeV trough-to-trough (T_T) periods since 1700. Regression coefficients are placed above the bracketed P-values. This data summary was derived from the R results in S8 Table. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

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Significant negative regression coefficients were obtained between cycle mean SIC and mean Cat.A&B outbreaks per cycle year (all B = -0.09 to -0.11, all P = 0.01, n = 26-27 SSN, GSSN, TSI, and CRI cycles), and with Cat.A and pandemics +/-epizoo outbreaks (B = -0.08 and -0.07, P = 0.03 and 0.04 respectively, n = 26 CRI cycles). A significant positive regression coefficient was obtained between cycle mean IAR and mean pandemics +/-epizootics per cycle year (B = 2.63, p = 0.04, n = 24 MeV cycles). By contrast, a significant negative regression coefficient was yielded between cycle mean IAR and mean epidemics +/-epizootics per cycle year (B = -1,97, p = 0.04, n = 27 TSI cycles).

A significant positive regression coefficient was obtained with mean CRI cycle anomalies and mean Cat.A&B outbreaks per cycle year (B = 0.23, P = 0.03) and with mean epidemics +/-epizoo per cycle year (B = 0.13, P = 0.01) for cycles defined by CRI T_T periods (n = 26). Significant positive regression coefficients were yielded for mean ^{10}Be cycle anomalies and mean epidemics +/-epizoo per cycle year (all B = 0.07-0.09, all P = 0.02-0.03, n = 27 SSN, GSSN, and TSI cycles). A significant positive coefficient meant there was an increased cycle outbreak rate (per year) as the cycle mean value increased above the RPM, and vice versa. Correspondingly, a significant negative coefficient meant there was a lower outbreak rate (per year) as the cycle mean value increased above the RPM, and vice versa.

Outbreak distribution by quartile grouping highlights risk factors

The mid-study (1750 +/-) broadly coincided with the coldest and lowest solar activity period, while the mid-RPM broadly coincided with the warmest and highest solar activity period, during the study period. The NHT°C anomaly (1500-2000) was at its deepest 30-year SMA trough in 1718 and at its tallest 30-year SMA peak in 1962, while the GT°C anomaly (1500-1993) was at its deepest 30-year SMA trough in 1775 and peaked in 1955 (30-year SMA). The ^{10}Be anomaly (1500-1994) reached its 30-year SMA peak in 1721 (period of lowest solar-/geo-magnetic activity) and its deepest trough in 1964 (period of highest solar-/geo-magnetic activity), while the TSI anomaly (1610-2018) reached its deepest 30-year SMA trough in 1675 and reached its 20th century peak in 1964.

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The percentage of negative independent variable anomalies and outbreaks associated with negative anomalies are detailed in Fig 6, which summarized co-plots of Cat.A&B outbreaks and all IVs (S9 Fig A-J, Supporting information). The majority of the temperature (GT°C 74%, NHT°C 90%) and solar activity variables (TSI 71%) were below or above (CRI 81%, ^{10}Be 68%) their respective 1961-1990 RPM. Forty-five of 49 (92%) outbreaks occurred before the RPM and three during the RPM (7.7%).

Fig 6. Percentage of negative anomalies and outbreaks associated with negative anomalies. This figure's data summarizes the linear plots for each independent variable and Cat.A&B outbreaks, which are contained in S9 Fig A-J. For perspective, the 1961-1990 RPM, by which most variable anomalies were derived, represented a period near the hot-end of a multi-century Arctic and Northern Hemisphere warming phase that started in the early-mid 18th century in the depths of the Little Ice Age (mid-study). Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

Chi-square (X^2) and Fisher's exact (Odds ratio, OR) test values associated with $p<0.05$ ("a significantly higher proportion"), and their degrees of freedom (X^2 all df = 1. OR all df = not applicable) are summarized in S10 Table and were derived from S11 Table, which applies to this section. A significantly higher proportion of categories comprising Cat.A outbreaks (SIC, 1500-, 1700-) and epidemics +/- epizootics (GSSN, 1500-) occurred with "*all negative versus all positive*" anomaly quartile-groupings. Significant test values were yielded for "*large negative versus all positive*" quartile-grouping proportions for epidemics +/-epizootics and NHT°C (1700-), TSI (1500-), and MeV (1700-). At the other extreme, a significantly higher proportion of outbreaks occurred with "*large positive versus all negative*" quartile groupings between epidemics +/-epizootics and IAR (1500-) and CRI (1500-, 1700-), and with MeV and pandemics +/-epizootics (1500-).

A significantly higher proportion of outbreaks occurred with "*large plus medium negative versus all positive*" quartile-groupings for categories comprising pandemics (SIC, 1500, 1700-) and with epidemics

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455 +/-epizootics (GSSN, 1500-). At the other extreme, significant test values were obtained for "*large plus*
456 *medium positive versus all negative*" quartile-groupings for categories comprising pandemics (GT°C, SIC
457 IAR, SSN, MeV, 1500- and/or 1700-). A significantly higher proportion of outbreaks occurred with
458 "*large plus medium negative versus large plus medium positive*" anomaly quartile-groupings for
459 Cat.A&B and GT°C (1500-, 1700-), epidemics +/-epizootics with GT°C (1500-) and MeV (1700-), and
460 with Cat.A&B and Cat.A and SIC (1700-).

461 # Multiple logistic regression confirmed outbreak predictors

462 This section reviews the best stepwise models (best models), and all best and short-listed models with ≥1
463 P<0.05 predictor (All-models) across all outbreak categories. This section refers to Table 3 and S12-13
464 Tables. Solar-/geo-magnetic and electromagnetic activity-related variables accounted for the majority of
465 significant and marginal predictors for All-models. Each category best model with the lowest AIC value
466 was achieved when IVs were smoothed between 9 and 11 years.

467 **Table 3. Multiple logistic regression best model and variance inflation factor summary results.**

(A) Lowest AIC, Outbreak category Pr(>|z|)<0.05, and <0.16	**β estimate sign: +ve or –ve**	**Cat. A&B**	**Cat. A**	**Pan***	**Cat. B**	**Epi***	**(B) Variance Inflation Factor (VIF)**	**Cat. A&B**	**Cat. A**	**Pan***	**Cat. B**	**Epi***	**Avg. VIF**
SA MAV period (years)		11	9	10	11	11							
Intercept	-ve												
10Be anom.	-ve				0.12	0.07	10Be anom.	3.7	2.9	3.0	**93**	22	**25**
CRI anom.	+ve				0.04		CRI anom.	12	7	8	**634**	30	**138**
MeV anom.	-ve					0.03	MeV anom.	3.0	2.5	2.7	**159**	8	**35**
TSI anom.	+ve				0.10	0.046	TSI anom.	3.7	3.3	3.5	30	9	**10**
NHT°C anom.	+ve						NHT°C anom.	15	10	11	35	32	**20**
GT°C anom.	-ve					0.10	GT°C anom.	5.2	4.3	4.9	61	8	**17**
SIC anom.	-ve	0.16					SIC anom.	3.0	3.2	3.2	11	4.5	**5.0**
IAR anom.	+ve				0.06	0.10	IAR anom.	1.3	1.4	1.4	11	2.2	**3.4**
SSN_dummy_P+T	+ve	0.04	0.049	0.04			SSN_dummy_P+T	1.0	1.0	1.0	2.1	1.2	**1.3**
AIC		150.8	135.4	124.5	31.5	52.5	**Avg. VIF**	**5.3**	**4.0**	**4.4**	**115**	**13**	**28**
Cox Snell pseudo-R2		0.03	0.02	0.02	0.08	0.06							
Number		219	229	224	219	219							

468 **(A)** Multiple logistic regression best model summaries for each outbreak category (all stepwise, backward method).
469 Each best model summarizes significant and marginal model predictors, provides the sign of the β estimate (positive
470 or negative impact on outbreak probability as the variable increases, and vice versa), and represented the lowest AIC

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value in its category. **(B)** The variance inflation factor (VIF) was used to assess multi-collinearity. Best model summaries from R are provided in the S12 Table and an All-model summary in S13 Table, which summarize all 55 short-listed models with ≥1 significant variable. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

Solar-/geo-magnetic and electromagnetic activity related predictors accounted for between 100% (Pr(>|z|)<0.05, 6/6 IVs, n = 5 models) and 69% (Pr(>|z|)<0.16, 9/13 IVs, n = 5 models) of all best model predictors, and between 78% (Pr(>|z|)<0.05, n = 43/55) and 67% (Pr(>|z|)<0.2, n = 80/120) of All-models. The SSN T01+P01 dummy variable was a significant predictor in all three best models and in 31 of 33 potential All-model occurrences, over the three categories comprising pandemics (Pr(>|z|)<0.2). In contrast, the SSN T01+P01 dummy variable was not a significant or marginal predictor for Cat.B and epidemic +/-epizootic categories in All-models. Contrastingly, CRI featured in 20/22 All-model potential occurrences with Cat.B and epidemics +/-epizootics (Pr(>|z|)<0.05). All three significant best model epidemic predictors were solar-/geomagnetic and electromagnetic activity related (CRI, MeV and TSI).

Climate change predictors did not feature to the same degree as solar activity related predictors in All-models. There were no significant best model climate change predictors (all Pr(>|z|) = 0.06-0.16, n = 4 of 13 IVs), while three of the four marginal climate change predictors were associated with categories comprising epidemics. However, climate change variables accounted for 22% (all Pr(>|z|)<0.050, n = 12/55) and 33% of All-model predictors (all Pr(>|z|)<0.2, n = 40/120), including SIC (n = 14), NHT°C and IAR (n = 10), and GT°C (n = 6) anomalies. Best model and All-model variance inflation factors (VIF) highlighted a complex issue of multi-collinearity with solar activity (CRI, MeV, 10Be, TSI) and climate change predictors (NHT, GTC, SIC, and IAR), especially with epidemic categories (see next).

Multi-collinearity implicated solar activity correlated climate change

Basic analysis confirmed normal data distributions (skewness within +/-2) and peakedness (kurtosis

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within +/-7) for all independent variables (S14 Table, Supporting information). Pearson correlation coefficients between regression model IVs (plus GMA-AA) are summarized in Fig 7A and 7B. Of 495 correlation permutations assessed 363 (73%) were P<0.001, 40 were p>0.001 and <0.05 (8.1%) and 92 were non-significant (19%). This correlation analysis highlighted medium-to-high correlations involving solar-/geo-magnetism (esp. CRI, ^{10}Be) and solar electromagnetism (TSI), with climate change variables: NHT°C with CRI, ^{10}Be, GMA and TSI anomalies; GT°C with CRI, ^{10}Be, GMA, NHT, SIC and SSN anomalies; SIC with GMA anomalies. These correlations increased with data smoothing (negative r: avg. r = -0.45 increased to r = -0.70, n = 9 comparators. positive r: avg. r = 0.43 increased to r = 0.65, n = 9 comparators, 1 to 11yr SMA (Fig 7A and 7B, S15 Table, Supporting information).

Fig 7. Pearson correlation coefficients between solar activity and climate change outbreak predictors. Graphically displayed Pearson correlation coefficients for key solar-/geo-magnetic variables versus solar-/geo-magnetic, solar electromagnetic, and climate change variables, and climate change versus climate change variables (1–11-year SMA, both variables). Correlation coefficients and associated data are provided to the right of each figure **(A)** and **(B)** legend and in the S15 Table. A linear- and scatter-plot of an 18-year SMA ^{10}Be versus NHT°C raw data anomalies (1406-1994) is provided in S16 Fig. This figure demonstrates that all Little Ice Age grand solar minimum periods paralleled a sustained NHT°C cooling, while these variables counter-tracked each other's large volatilities over decadal to centennial time scales up to the post-RPM period. Data citations: Independent variable data [55], [57]–[60], [62]–[65].

The best model[1] and All-model[2] mean variance inflation factors for CRI (VIF = 138[1], 41[2]), MeV (VIF = 35[1], 12[2]), 10Be (VIF = 25[1], 6[2]), NHT°C (VIF = 20[1], 13[2]), GT°C (VIF = 17[1], 7[2]), and overall (mean VIF = 28[1], 10[2]) are provided in Table 3B[1] and S13 Table[2] (B). Multi-collinearity was most evident with Cat.B outbreaks (mean VIF = 115[1], 32[2]) and epidemics +/-epizootic (mean VIF = 13[1], 7[2]), two-thirds of which originated in Europe. This level of multi-collinearity indicates potential suppressor-interaction effects between model predictors. This high VIF data (>10) reflects the high-increasing Pearson correlation

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coefficients (from 1 to 11-year SMA) between the solar-/geo-magnetic proxies, especially CRI (assessed at earth's orbit) and 10Be (Greenland ice core derived), with the terrestrial-derived climate change proxies NHT°C (Greenland ice core derived), SIC (Arctic), and GT°C (Greenland ice core).

Re-calibrating outbreak risks relative to the Climate Optimum

This section refers to Fig 8, and S17 Table and S18 Fig (16 annotated ice core temperature plots). The Little Ice Age (LIA) GT°C temperature nadir was reached by mid-study in 1761, which occurred 7,771 years after and was -5.9°C below the Holocene Climate Optimum (HCO) peak temperature (6010 BCE) [64]. The Vinther 11,700-year Greenland ice core LIA temperature nadir was reached in 1700, which occurred 7,680 years after and was -4.9°C below the HCO (5980 BCE) [67]. Similarly, the mean of nine Greenland ice cores (Buizert) show the LIA temperature nadir was reached 1802 (SD = 72 years), which occurred a mean 7,307 years after (SD = 920) and was a mean -5.0°C (SD = 1.0°C) below the HCO peak temperature. This mean 5.0°C decline represented 21% of the prior Holocene interglacial increase in absolute terms. During the Holocene interglacial period the temperature increased by a mean 23.1°C in a mean 9,844 years (mean LGM 15,349 BCE and HCO 5,504 BCE) [69].

Fig 8. The GT°C mid-study climate benchmarked against 15 polar ice cores. (A) Temperature changes between glacial cycle landmarks are provided for 16 polar ice cores, including the GT°C data used in this outbreak risk factor study. Inter-landmark periods include: (i) the Holocene interglacial period between the Last Glacial Maximum (LGM) and Holocene Climate Optimum (HCO), or the coldest glacial cycle (GC) temperature to the hottest temperature (or anomaly, °C), (ii) the HCO to Little Ice Age (LIA) temperature nadir, or peak glacial cycle temperature to lowest temperature after the HCO during the LIA period. **(B)** The ice age entry percentage corresponds with the temperature decline between the HCO and LIA (by mid-study) divided by the Holocene interglacial temperature increase between the LGM and HCO. See S17 Table for the data table underpinning these graphics. Data citations: Polar ice core data [64], [67]–[73].

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From the LIA temperature nadir (1761) to mid-RPM (1975) the GT°C then increased 1.5°C in 214 years, and the Vinther Greenland ice core temperature increased 2.3°C in 260 years from 1700. This means that by 1975 and 1960 Greenland was still 4.4°C and 2.5°C colder than at the HCO 7.8kyr and 7.7kyr beforehand respectively. The Buizert Greenland ice cores showed a mean 2.4°C increase in 178 years from the LIA temperature nadir to the mid-RPM (SD = 0.3°C, n = 9). Despite this warming oscillation, Buizert's nine Greenland ice cores were still a mean 2.6°C lower (SD = 1.0°C) than at the HCO peak temperature 7.5kyr prior, or 11% of their mean Holocene interglacial increase in absolute terms.

In Antarctica, the temperature declines between the HCO peak temperature and LIA temperature nadir at Dome-C (Jouzel), Vostok (Lorius), Dome Fuji (Uemura) represented 36%, 19% and 15% respectively of their respective Holocene interglacial increases in absolute terms.

Discussion

In general, across all analytical methods (1500-, 1610-, 1700-), pandemics (with a SSN P01+T01 trigger) and epidemics (with a +CRI anomaly trigger) were associated with periods of sustained (1-11 years, 11-year cycle means) and/or extreme +/-medium quartile periods of: (1) low solar-/geo-magnetic activity (proxied by +CRI, +10Be, -MeV, -SSN, and -GSSN anomalies) and electromagnetic activity (proxied by –TSI anomalies), and (2) cold-glaciating climate change implicating Greenland (proxied by -GT°C, -SIC-algal growth, and +IAR anomalies) and Northern Hemisphere regions (proxied by -NHT°C anomalies).

Four categories of outbreak risk factors putatively implicating "immunological susceptibility and induced immunosuppression" were identified. These included 11-year solar cycle extremes, low solar and geomagnetic activity, Arctic cold and glaciation (*mid-study was the coldest-iciest period 8-kiloyears after the glacial cycle peak temperature*) and geographic risk (*Europe, North America, Russia, China*). The database and each risk factor are reviewed and compared with prior studies and given relevant context via the literature. The putative means by which risk factors were linked to "immunological susceptibility and

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regional-scale induced immunosuppression" are also reviewed.

Influenza outbreak database review

On a comparable basis since 1700, this study's database method confirmed geographical extent for 25 pandemics and nine regional epidemics, and detailed 15 concurrent epizootics/zoonosis (seven reviews). This compared with Tapping's 15-21 pandemics (two reviews), Ertel's 25 pandemics (10 reviews), Yeung's 15 pandemics and possible pandemics (five reviews), while Qu utilized Yeung's uncertain list. This methodology resolved expert review differences in outbreak classifications (9 instances), while eliminating uncertainty for 21 instances of 'possible' pandemics in 157 pooled outbreak assignations. In line with all prior studies and historical records, stated outbreaks may not all have been influenza-A, but could have been other pathogens behaving like and described as influenza. This pathogen-etiology uncertainty was more likely before 1700 due to heterogeneous disease terminologies and a relative paucity of detailed records by physicians. This inherent uncertainty directed the dual analysis from 1500- and 1700- (3/5 analytical methods started from 1700 anyhow).

A surprise discovery was that since 1500 both pandemics *and* regional epidemics were frequently associated with concurrent influenza epizootics (76% equine associated), which was not significantly different in frequency between these outbreak categories. This concurrent-equivalent epizootic finding between pandemics and epidemics goes against conventional wisdom, in which epidemics were said to be associated with viral mutation of seasonal-endemic IAV subtypes (antigenic drift), while pandemics were said to be associated with zoonosis and/or IAV reassortment (antigenic shift) [6], [10], [89]. This finding indicates some regional epidemics +/-epizootics were different from seasonal-endemic influenza. Alternatively, they could have represented outbreaks whose global spread was thwarted, or represented Europe's special case with epidemics (see discussion on multi-collinearity), or epidemics before 1825 were pandemics incompletely recorded in the global record (mild outbreaks), or combinations thereof.

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Outbreak timing risk factors (solar cycle peaks and troughs)

Pandemics were periodically inescapable on an 11-year solar cycle basis, while solar cycles were relatively predictable. There was roughly one pandemic per 11-year solar cycle since 1700, with three-quarters of these occurring within one year of the cycle peak and trough. There was good agreement between simple and multiple logistic regression in identifying sunspot number P01 and/or T01 solar cycle stages as timing risk factors. Multiple regression analysis confirmed the SSN P01+T01 dummy variable as a significant pandemic predictor in all three best models and 31/33 short-listed models, suggesting SSN cycle extremes +/- 1-year were a pandemic *trigger*. By contrast, significance was not achieved for P01+T01 stages with epidemics (all 22 models), potentially reflecting the smaller numbers of epidemics compared with pandemics (n = 9 -v- 25, 1700-) and/or having different triggers (CRI, see geographic risks). These results confirm Hope-Simpson's original observation on pandemic peak timing, and study conclusions by Tapping, Ertel, Yeung, and Qu claiming a link between SSN extremes and pandemic risk.

The theoretical case for solar-/geo-magnetic modulation of circadian-immuno-inflammatory biology merits consideration in explaining this timing risk data. As introduced, an 11-year SSN P01+T01 concentration of outbreaks potentially implicate changes in solar magnetic polarity and/or heliospheric magnetic flux [14], [17], [61]. Theoretically, magnetoreceptive cryptochrome regulatory proteins (repressors) interacting with circadian core molecular clockwork (CLOCK-BMAL1) offer a means by which geomagnetism could modify immuno-inflammatory biology [18]. Cryptochromes are highly conserved ancient-ubiquitous photoreceptor flavoproteins containing two non-covalently bound chromophores: a redox-active flavin adenine dinucleotide (FAD) and a light-harvesting cofactor. Cryptochrome signaling is tied to the photoreduction of FAD, whose spin chemistry is magnetoreceptive in an effect known as a *radical-pair mechanism*. The feasibility science for magnetoreceptive cryptochrome modulation operating within weak geomagnetic fields was expertly reviewed in the context of bird migration and plant models [19], [20], which highlights its potential for outbreak risk involvement.

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Geographical related outbreak risk factors

This study showed that Europe, North America, Russia, and China originated 81% of all pandemics (n = 25/31, 1500-), while Europe (2/3rd) and North America (1/3rd) accounted for all epidemics. Historical outbreak reviewer constraints-bias and incomplete record coverage pre-1700 cannot be ruled out. However, other potential causes also exist that implicate Northern Hemisphere (>30-40°N) and Arctic latitudes, and possibly bird migration cruising altitudes over these latitudes. Prior solar activity-pandemic risk factor studies and the seven expert reviews didn't quantitatively assess geographical risks.

Single nucleotide polymorphisms (SNP): One hypothesis is that certain race-ethnicities (Caucasian, Chinese) with innate-/early adaptive- immunity SNP(s) [26], [27], [90], [91], and devoid of preexisting protective-adaptive immunity (Bcell and/or Tcell), were *doubly susceptible* to novel-zoonotic IAV infections. Such people, if in contact with horses, poultry-migrating birds, animal markets and processing [13], [92], could have represented the primary zoonosis doorway and early human-to-human IAV transmission "breeder" population (family clusters +/-SNPs) [93], [94]. In such people-families, Bottleneck-1's biology could have been more readily surmounted if they were rendered immunosuppressed by regional-scale stressors impacting their circadian (P01+T01 solar-/geo-magnetic trigger) and immune systems (cosmic rays, cold stress). Concurrent with surmounting Bottleneck-1's biology, regional viral transmission could have been facilitated in an immunologically susceptible population (Bottleneck-2), if also rendered immunosuppressed (geomagnetism, cosmic rays, cold stress).

Regional modulation of atmospheric cosmic ray entry and ionization: Cosmic ray intensity was a significant predictor (trigger) in 20/22 All-model potential occurrences for Cat.B and epidemics +/- concurrent epizootics, and in 24/55 significant predictors across all five-outbreak categories. Two-thirds of epidemics originated in Europe and the balance largely in Nth America. Geographical risk could have arisen in these regions associated with differentials in solar- and/or geomagnetism and cosmic ray ionization, in geographical latitudes-altitudes relevant to outbreaks and animal-IAV reservoirs.

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Magnetic latitude defines a critical threshold (cut-off rigidity) below which cosmic rays of a lower energy cannot enter the atmosphere. Therefore, more cosmic rays penetrate the atmosphere at higher magnetic latitudes and with higher energies, thus increasing northern-regional cosmic-ray ionization [61]. Furthermore, variations in earth's magnetic dipole axis were associated with substantial regional differences in geomagnetic field strength and cosmic ray-induced ionization (CRII), with a maximum CRII during the Maunder minimum in Europe (1640-1720). Strong correlations between CRII and low cloud cover also existed (cooling link), limited to the northern Atlantic and Europe, Far East, and Antarctica [31]. Thus, increased CRI/CRII could have impacted geographically relevant regional climate change, in-flight bird risks, and animal-IAV reservoirs and human populations (immunosuppression).

Regional scale cosmic ray induced immunosuppression: The literature highlights two links between increased cosmic rays and disease biology. Firstly, cosmic rays and ionizing radiation (IR) linked to *immunosuppression* are detailed in the space environment, radiotherapy, and environmental epidemiology literature [28], [29]. Immune response effects (lymphocytes, cytokines, cellular markers) were seen at low chronic exposure rates above and below 1mSv/year (milli-Sievert, international unit of radiation absorption), and with very low doses of radon gas radiotherapy (0.3 mSv) [29]. The global mean human cosmic radiation dose was estimated at <0.4 mSv/year [95]. This collectively indicates a *low threshold* for immunological sensitivity to cosmic radiation. More generally, natural killer cells (innate immunity) and lymphocytes (adaptive immunity) appear most sensitive to IR [96], [97]. Acute low doses alter lymphocyte and cytokine responses [98], [99], while therapeutic IR modulates important immuno-molecular control pathways [100], which are also coopted by IAVs during infection (NF-κB).

Secondly, there is evidence of *increased disease mortality* in magnetic anomaly regions. Significant correlations exist between annual CRII flux (0.2 mSv/year) and mortality rates in Sao Paulo, including infectious disease mortality. During 11-year solar minima when CRII was high there was a significant increase in mean mortality rates [30]. Sao Paulo resides in the South Atlantic Anomaly (760m above sea

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level, asl.), or Earth's weakest magnetic field and largest sink for cosmic high-energy particles [101].

For clarity, there is no need to invoke cosmic rays as the cause of IAV mutation underpinning pandemics [43], [46], [47]. This is because IAVs are inherently error-prone during replication (epizootics, zoonosis, epidemics, pandemics, endemics), while the selection pressure imposed by antibody immunity and MHC and HLA system polymorphisms (animal and human genetic diversity in T-cell immune responses) naturally drives viral evolution [25], [50], [102]. The integration of faulty nucleotides occurs at an innate high rate yielding 2–3 nucleotide substitutions per replicated IAV genome [103], [104]. Thus, the opportunity for geographically expansive transmission-optimizing viral evolution is ever-present once a novel-zoonotic IAV replicates itself in sufficient titers to infect another person (or family cluster) for the first time (Bottleneck-1).

Animal IAV reservoirs: The source of novel-zoonotic IAVs could also have represented a geographical risk linked to equine and/or avian ecology. *First IAV source*: Forty-three percent (n = 21/49) of influenza outbreaks since 1500 were associated with concurrent epizootics (n = 16/21 equine) (Fig 2B). Morens and Taubenberger tell us, "regardless of geographic locale, equine influenza typically appeared about three weeks before human influenza" [8]. This high concurrency of equine and human outbreaks does not prove zoonosis. However, it does indicate the presence of a novel influenza-like pathogen undergoing epizootic transmission (implying MHC-driven mutation-recombination) in a species placed under *physiological stress* in proximity to humans (transport, work, and war). Human challenge studies with equine influenza virus (EIV) [105], [106] and a review (plus others) confirm the zoonosis potential of EIVs [107].

Mongolia spotlights a potential historical geographic hotspot for seeding other horse populations and/or IAV zoonosis. A large horse and wild ass population still exist in Mongolia with preexisting immunity to avian H1, H3, H5, H7, H8, and H10 IAVs introduced during bird migration stop-overs [108], [109]. This indicates cross-species IAV transmission occurred, likely enabled by abundant avian-like α-2,3-sialic acid receptors in the equine upper respiratory tract. It was suggested horses could have historically represented

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an IAV intermediate host [110]. Such geographic hotspots could have been replicated across Europe, North America, and Eurasia during the Little Ice Age, when horses were more abundant than today.

Second IAV source: Even though migrating birds did not feature like horses in the concurrent epizootic data, their potential contribution to equine intermediate hosts before zoonosis (IAV mammalianization) and direct zoonosis pre-1900 cannot be ignored. After all, avian IAVs contributed from 1-8 genes to each 20th-century pandemic since 1918, and both avian H5N1 and H7N9 zoonosis [8]. Migratory birds are also natural hosts to most IAV strains, making them a dynamic-interchanging viral gene pool reservoir with regional-global reach. Millions of migratory birds biannually flew over northern temperate and high geomagnetic Arctic latitudes (mean altitude 0.5-1.5km, maximum 3–5km asl.) [111], [112]. Thus, physiologically stressed birds carrying IAV strains spent hundreds of hours flying their geomagnetically sensitive physiologies and annually-varying immune systems [113]–[115] through increased cosmic ray levels, varying geomagnetic fields and storms, and much colder temperatures than terrestrial IAV hosts. Bird migration, therefore, increased their circadian-immune system exposure to all outbreak risk factors.

Recent avian epizootics with highly pathogenic H5N1 also highlight how Arctic cold winter weather breakouts impacted wild bird migration and over-wintering epidemics in Europe and Eurasia, and how these diseased birds posed risk to intensively (stressed) farmed animals [116]–[118].

Indirect outbreak risk factors mediated by solar activity

The same solar-/geo-magnetic activity (proxied by CRI, 10Be, MeV, SSN, and GSSN) and solar electromagnetic activity (proxied by TSI) variable anomalies identified as outbreak risk factors, plus GMA-AA, were also significantly correlated with the Greenland and Northern Hemisphere climate change outbreak risk factors (proxied by NHT°C, GT°C, SIC, IAR), which increased with data smoothing. A strong correlation between the NHT°C raw data and 18-year SMA ^{10}Be concentration anomaly risk factors (1406-1994) indicates the NHT°C followed sustained changes in solar-/geo-magnetic activity. In fact, all extended cooling phases during the LIA coincided with grand solar minimum periods (S16 Fig).

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Multiple regression models highlighted an issue with multi-collinearity, which like the correlation data increased with data smoothing (11yr SMA > raw data). Multi-collinearity strongly implicated solar-/geo-magnetism (CRI >>> MeV >> 10Be) over climate change variables (NHT°C > GT°C), and mainly with epidemic categories (Cat.B > epidemics), which predominated in Europe > North America. Potential model CRI suppressor interactions are indicated by this high multi-collinearity, which is supported by all best model climate change variables being non-significant (all Pr>|z| = 0.051-0.2). This contrasted with GT°C, NHT°C, SIC, and IAR being significant predictors in simple logistic and linear regression analyses.

The above points to a *statistical confirmation* that solar-/geo-magnetic activity was also an indirect outbreak risk factor via its correlated-impact on climate change, explaining the high multi-collinearity. This putative climate change link during the study period is well supported by the literature.

A body of science promulgates a planetary gravitational and inertial influence on the sun (solar dynamo), which control cycles of solar magnetized wind and irradiance emissions. This planetary influence also modulates the Earth–Moon system, which is theorized as a coupled orbital-rotational-energy exchange system (Pattern Recognition in Physics [119]). Magnetized solar wind modulates CRI (at earth's orbit), and magnetospheric shielding of atmospheric cosmic ray entry (proxied by terrestrial ^{10}Be and ^{14}C), which in turn modulates low cloud cover (climate change) [32]. Magnetized solar wind also modulates earth's rate of rotation, which impacts atmospheric circulations (weather systems) and ocean circulations (heat-energy transfer, climate change), geomagnetism (cosmic ray entry-ionization, dipole axis movement), and periodic tectonic-volcanic activity (climate forcing volcanism) [120]–[124].

In addition to the above described climate change mechanisms, the literature also describes the solar-/geo-magnetic modulation of regional climate change during the Little Ice Age and study period. Strong cooling with +/-extremes of precipitation was observed in the North Atlantic and northern latitudes of Europe [125]–[127], China [128]–[131], and North America [126] [127], plus other regions. This regional climate change impact was mainly correlated with solar-/geo-magnetically modulated cosmogenic

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radionuclide data (^{10}Be, ^{14}C) and changes in atmospheric-weather circulations (location, phase, intensity). Likewise, Arctic drift ice changes over the last 11,000 years, including the last big LIA advance, were also correlated with cosmogenic radionuclide data (^{10}Be, ^{14}C) [134]. Sustained Arctic sea ice expansion during the LIA also implicated periodic climate-forcing volcanism [135]–[137].

Therefore, in addition to solar-/geo-magnetic activity and cosmic rays putatively impacting circadian-immuno-inflammatory biology (*direct outbreak risk factors*), solar activity correlated climate change also impacted IAV-host biology indirectly via its control over regional weather systems and climate change (*indirect outbreak risk factors*). Periods of colder NHT°C and GT°C (-ve anomalies) and Greenland glaciation (-SIC-algal growth, +IAR anomalies) are assumed to have been reflected regionally in European, Eurasian, and North American weather systems, and in modifying migrating bird habitats, over-wintering, and migration. In so doing, regional-scale cold stress would have immunosuppressed animal and human populations, while cold climate change (modulating temperature-humidity) would have assisted regional-scale infectious aerosol transmission and dried out animal and human respiratory mucosal surfaces to aid viral entry and replication.

Outbreak risks linked to the glacial cycle stage

A fourth risk factor is comprehensible when the study period is given a glacial cycle context relative to the Holocene Climate Optimum (HCO), versus an arbitrary 1961-1990 RPM (per scientific norms) at the *hot end* of a multi-century warming *oscillation* initiated mid-study. By mid-study Greenland was at its coldest post-HCO temperature (mean -4.8°C, n=10 ice cores), or -21% of its prior Holocene interglacial increase (mean +23.3°C) [68], [69]. These post-HCO Greenland temperature declines were comparable to the shorter Kobashi GT°C (-5.9°C) and Vinther (-4.9°C) ice cores (11.5kyr and 11.7kyr respectively) [64], [67]. This devolving-oscillatory temperature decline in Greenland post-HCO as a percentage of the prior interglacial increase was similar to Antarctica (-15% to -36%). After the LIA temperature nadir Greenland then entered a multi-century warming oscillation, which paralleled an unprecedented (in 8kyr)

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increase in solar activity [138]. However, even by mid-RPM Greenland temperatures were still 2.5°C-4.4°C colder than at the Arctic HCO, meaning the hottest period on record was *history*.

The literature confirmed the above data and showed the warmest Arctic period since the Last Glacial Maximum (approx. 18kyr ago) occurred from 8-5kyr ago, with temperatures 2-4°C hotter than today [139]–[141]. The Greenland temperature decline after the HCO paralleled a sustained 40-50 Watt/m^2 decline in precession modified solar insolation at 60-65°N [142]–[144], or circa 15-times the theoretical radiative-forcing impact of carbon dioxide at today's output level (3 Watts/m^2) [145]. Abrupt-periodic Arctic neoglacial advances also started about 5kyr ago, with northeast Greenland perennially ice-locked from 3kyr ago [146], [147]. Five millennia of Arctic glacier advances peaked in size in the *middle of this study period* [1], [2]. In Antarctica, the HCO period took place from 11.5-9kyr ago, with a secondary optimum 8-5kyr ago. Periodic post-HCO glacier advances also occurred in Antarctica [141], [148], including the Antarctic Peninsula [149], [150]. Much of this neoglacial ice melted after the LIA temperature nadir and Maunder minimum (1685 = deepest SSN trough in 7.2kyr), along with an unparalleled increase in solar magnetism in 8kyr (C^{14} derived SSN) [138].

The above indicates earth *entered a new ice age* after the Holocene Climate Optimum, and the Poles were near the peak of a solar and geomagnetic activity controlled multi-century warming oscillation at the RPM. Since the HCO peak temperature 8kyr ago, all temperature oscillations switched to a cooling phase, indicating a post-RPM *ice age re-entry* has a certain probability. This probability is supported by solar activity-climate experts who predicted a grand solar minimum trough between 2040 and 2060 and a return to a Little Ice Age-like climate [123], [151]–[155]. This has implications for 21st century pandemic influenza risks.

Conclusion

This environmental immunology study addressed a crucial knowledge gap in influenza pandemic risk

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factor understanding. Influenza pandemics were triggered by 11-year solar cycle extremes, potentially implicating solar-/geo-magnetic activity repression of magnetoreceptive circadian core molecular clockwork (immune and inflammatory system controller), concomitant with influenza virus replication that evolutionarily coopted the circadian system. Influenza pandemics and regional epidemics were associated with periods of sustained and/or extreme low solar and geomagnetic activity and cold-glaciating climate change (Arctic, Northern Hemisphere), potentially implicating regional-scale cosmic ray and cold-stress induced immunosuppression, and enhanced infectious aerosol transmission and respiratory mucosal drying. Europe[1], North America[1], Russia, and China originated most pandemics and all regional epidemics[1], potentially implicating latitudinal-dipole-altitudinal differentials in cosmic ray induced ionization (immunosuppression, cold climate change), ethnicity-related host immuno-genetics (susceptibility), and equine-avian viral reservoirs and ecology. This collectively aided viral entry and replication in immunologically susceptible animals (epizootic-driven pre-zoonotic IAV variants), people (zoonosis, family clusters), and populations (pandemics, epidemics). Solar-/geo-magnetic mechanisms of influenza pandemic risk (incl. climate change), and our stage of the glacial cycle are not currently anticipated. Prepandemic immunization [156]–[159] utilizing approved influenza vaccine technologies to generate broadly cross-reactive antibody herd immunity [160]–[162]) could mitigate immunological susceptibility and induced immunosuppression (to H5N1, H7N9 etc.) during this high-risk grand solar minimum period.

Acknowledgements

I would like to thank Oleksii Sukhoi, a freelance statistician (UpWork) for his collaboration with study methodologies, for conducting data analysis in R, and for reviewing the final Excel file and manuscript methods and results for technical accuracy.

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Supporting information captions

S1 Table. Influenza pandemic, regional epidemic, and epizootic database summary (1500-2018).

This influenza outbreak database summary details various categories of influenza pandemics and regional epidemics since 1500CE. Key information was summarized from expert reviews and their pooled review-cited publications (where available online without fee), including the outbreak start dates, expert review confirmation of 'influenza', reviewer assigned (provisional) and final adjudicated outbreak categorization, geographic extent and origination, association with concurrent epizootics/zoonosis, plus other medical-epidemiological information (databased, not provided in S1 Table). See the readme file (Figshare) for a detailed description of the database methodology. Data citation: Outbreak database expert review citations [5]–[11].

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S2 Table. Logistic regression summary results comparing solar cycle stage groupings of outbreaks.

Regression beta coefficients, P-values, stage probabilities, Odds ratios and 95% lower and upper confidence interval results for solar cycle stage grouping comparisons for SSN, GSSN, and TSI cycles, with outbreak categories comprising pandemics (Cat.A&B, Cat.A, Pandemic +/-concurrent epizootics). Solar cycle stage groupings comprised the peak +/- 1-year (P01), trough +/- 1-year (T01), and P01+T01, versus the combined inter-peak-to-trough plus inter-trough-to-peak stages. These results were derived from S3 Table (R output results). See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55], [56], [62].

S3 Table. Logistic regression results comparing solar cycle stage groupings of outbreaks (R output).

Logistic regression coefficients (betas), P-values, Cox Snell pseudo-R-squared, standard errors (SE), Akaike information criterion (AIC) results exported from R (with formatting). This data was used to derive the solar cycle stage grouping probabilities and Odds ratios for influenza outbreaks (categories comprising pandemics), within SSN, GSSN, and TSI 11-year solar cycles. Investigatory stage groupings comprised the peak +/- 1-year (P01), trough +/- 1-year (T01), the combined peak and trough +/- 1-year (P01+T01), versus the combined inter-peak-to-trough plus inter-trough-to-peak stages (P_T+T_P). See the readme file (Figshare) for a detailed description of the methodology. Data sources: Outbreak database expert reviews [5]–[11]. Independent variable data [55], [56], [62].

S4 Table. Number, proportion, and percentage of influenza outbreaks by solar cycle stage grouping.

The number, proportion, and percentage of influenza outbreaks by 11-year solar cycle stage grouping for cycles defined by SSN, GSSN, and TSI periods, for different categories of influenza outbreaks (Cat.A&B, Cat.A, pandemics +/-concurrent epizootics or Pan*+/-Epi, and epidemics +/- concurrent epizootics or Epi*+/-Epi). The proportion of outbreaks was calculated as the stage group years with outbreaks divided by the total stage group years*100. Percentage of outbreaks per stage grouping was calculated as number of years in a stage with outbreaks divided by the total outbreak years across all stage groupings. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable

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data [55], [56], [62].

S5 Table. Solar cycle stage grouping comparisons between pandemics and epidemics.

Fishers exact test results (Odds ratios and P-values) for an array of solar cycle stage-grouping comparisons between pandemics* and epidemics*. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[58], [62].

S6 Table: Simple logistic regression results (2-11yr SMA, non-timing risk factors).

Coefficients of simple logistic regression, P-values, standard errors (SE), Z-statistics, Cox Snell pseudo-R-squared, and Akaike information criteria (AIC) results downloaded from R. A simple bivariate logistic regression was used to investigate the impact of a single independent variable (2-11 year SMA) in explaining the variability of the dependent variable (outbreak category) between 1500 or 1700, and 2018, in case the outcome was binary. See the readme file (Figshare) for a detailed methodology description. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S7 Table. Solar cycle and influenza outbreak per cycle metrics.

The assessment period, number of cycles, the cycle mean duration and standard deviation for SSN, GSSN, TSI, CRI, and MeV trough-to-trough cycles are detailed. The mean of mean number of influenza outbreaks per year and standard error (SE), and the mean interval by outbreak category comprising pandemics are also detailed. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Solar cycle data citations [55]–[58], [62].

S8 Table: Simple linear regression results (cycle mean variable anomaly, cycle mean outbreaks/year).

Non-standardized and standardized linear regression coefficients, Pr(>|t|)<0.05, standard errors (SE), T-values, Cox Snell pseudo-R-squared values, F-statistic values, and F-stat degrees of freedom (DF) results output from R. Simple

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linear regression was used to investigate if the mean number of outbreaks per solar cycle year (dependent variable) could be predicted by the cycle mean independent variable, for cycles defined by SSN, GSSN, TSI, CRI, and MeV trough to trough periods. The asterix above pandemic* and epidemic* means +/-concurrent epizootics/zoonoses. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S9 Figure. Linear plots of independent variables with Cat.A&B influenza outbreaks.

Cat.A&B outbreaks were plotted relative to: **(A)** sunspot number (SSN), **(B)** group sunspot number (GSSN), **(C)** total solar irradiance (TSI), **(D)** cosmic ray intensity (CRI), **(E)** Northern Hemisphere temperature (NHT), **(F)** Greenland temperature, **(G)** sea ice cover (SIC), **(H)** Greenland ice accumulation rate, **(I)** solar modulation function (MeV), **(J)** Beryllium10 concentration (^{10}Be) anomalies (except SSN and GSSN, which use the raw data). Generally accepted grand solar minimum and maximum periods (A-C), and the 1961-1990 RPM (A-J) are graphically annotated. See the readme file (Figshare) for a detailed description of the methodology used to calculate anomalies and create the graphics. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S10 Table. Outbreak proportion and variable anomaly quartile grouping comparisons.

Statistically significant Chi-square statistic (degrees of freedom, df=1 in all cases) or Fishers exact test Odds Ratio results (underscored, df=not applicable), with P-values placed below them (in brackets)(na=not applicable). These results are presented for an array of significant outbreak proportion and variable anomaly quartile grouping comparisons, which differed by sign and magnitude. This data was derived in R from S11 Table data. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S11 Table. Numbers of outbreak and non-outbreak years by +/- variable quartiles.

Tables **(A)** from 1500-, and **(B)** from 1700-, provide the numbers of outbreak (event) and non-outbreak (event) years

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by positive and negative quartile for each independent variable and outbreak category. These results were generated by R, and were used to derive the Chi-square and Fisher's exact tests of independence results in S10 Table. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S12 Table: Multiple logistic regression best model results (stepwise, backward method).

Multiple logistic regression best model summary results for each outbreak category comprising ≥1 significant predictor ($Pr(>|z|)<0.05$) and any associated marginal predictors ($Pr(>|z|)<0.2$), estimates of the β coefficients (positive or negative impact on outbreak probability), standard errors (SE), Z-values, Akaike information criteria (AIC), Cox Snell pseudo-R-squared, and variance inflation factor (VIF) data. Best models had the lowest AIC value in their category and ≥1 significant predictor ($Pr(>|z|)<0.05$) +/- marginal predictors. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S13 Table. Multiple logistic regression and variance inflation factor results summary (All-models).

(A) This All-model summary comprises all stepwise models (backward method) with ≥1 significant predictor ($Pr(>|z|)<0.05$), and their associated marginal predictors ($Pr(>|z|)<0.2$), by outbreak category (Cat.A&B, Cat.A, pandemics +/-concurrent epizootics or Pan*, epidemics +/- concurrent epizootics or Epi*, and Cat.B). Outbreak and predictor category totals highlight the relative dominance of predictors, and the contrasting differences between pandemic and epidemic outbreak categories. **(B)** An All-model summary of the variance inflation factor (VIF) data highlights an issue with multi-collinearity. A VIF>10 was considered problematic, a VIF>5 was highly correlated, and a VIF>2.5 was moderately correlated. See the readme file (Figshare) for a detailed description of the methodology. Data citations: Outbreak database expert reviews [5]–[11]. Independent variable data [55]–[59], [62]–[65].

S14 Table. Basic statistical analyses results for independent variables (outbreak risk factors).

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Basic statistical parameters were calculated in Excel from the raw and anomaly data. Both ^{10}Be and IAR (same dataset) had 14 years of missing data (in their 495 year data series, 1500-). A detailed description of the missing data and how this was managed is explained in the readme notes available online (Figshare). Data citations [55]–[59], [62]–[65].

S15 Table. Correlation coefficients between solar activity and climate change outbreak predictors.

Pearson correlation coefficients and P-values, and other results are provided for key solar-/geo-magnetism (esp. CRI, 10Be, GMA-AA) and solar electromagnetism variables (TSI), between themselves, and with terrestrial-derived climate change variables (NHT°C, GT°C, SIC, and IAR anomalies). These results demonstrate the impact of data smoothing on increasing the correlation coefficient values, which mirrors the trend with the variance inflation factor data for these same variables. The table is split into positive (N = 9 columns) and negative (N = 9 columns) correlation coefficients. A summary of the mean absolute and percentage increase in correlation coefficients from the raw data to the 11-year SMA are provided below each column. This data was used to create the publication Fig. 7. See the readme file (Figshare) for a detailed description of the methodology. Data citations [55], [57]–[60], [62]–[65].

S16 Figure. Northern Hemisphere temperature -v- 18yr SMA ^{10}Be conc. anomalies (1406-1994).

(A) This figure depicts a linear plot between the NHT°C raw data and an 18-year SMA ^{10}Be concentration anomaly. This graphic is annotated with period-specific Pearson correlation coefficients relevant to the whole period (1406-1994, r=-0.75), to three of the Little Ice Age's (LIA) numerous grand solar minimum periods (Spörer, Maunder, and Dalton), and from the beginning of the Gleissberg–Gnevishev minimum (1898-1923) that straddled the deadliest influenza pandemic on record (1918-20) to after the 1961-1990 RPM. These co-plotted variables' decadal- to centennial-scale oscillations also counter-tracked each other through both cold and warm climate phases, including through the industrial-modern era (1899-1994, r=-0.85). All LIA grand solar minimum periods paralleled a sustained NHT°C cooling period. **(B)** Figure A converted into a scatter plot and annotated with a trend line, slope equation and R-squared value. **(C)** A series of Pearson correlation coefficients were derived for multiple permutations of the raw data and trailing simple moving average periods for both variables (11, 18, 24, 30, and 36

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years). This analysis was used to select the 18-year SMA ^{10}Be concentration anomaly versus NHT°C raw data for plotting (quasi-optimized correlation), and demonstrated the impact of data smoothing. This smoothing was used to proxy a potential sustained cause (^{10}Be, solar-heliospheric-magnetospheric magnetism controlled) and effect (NHT°C, terrestrially derived from Greenland ice core raw data). See the readme file (Figshare) for a detailed description of the methodology. Data citations [59], [63].

S17 Table. Re-calibrated mid-risk factor study period relative to the Holocene Climate Optimum.

Immutable glacial cycle landmark temperatures and their changes and intervals are provided for 16 polar ice cores, which were used to benchmark and re-calibrate this risk factor study's GT°C temperature data relative to the glacial cycle's maximum and minimum temperatures versus the 1961-1990 RPM. This data was extracted from the datasets cited below and is graphically depicted in its entirety in S18 Figure A-P. The ice age entry percentage (right shaded column) corresponds to the temperature anomaly decline between the Holocene Climate Optimum (HCO) and the Little Ice Age temperature nadir (LIA, mid-study), divided by the Holocene interglacial temperature increase between the Last Glacial Maximum (LGM) and HCO. For analytical purposes, temperatures were measured from their deepest troughs to their tallest peaks. The Holocene interglacial period represented the period between the LGM and HCO, which corresponded with the interval between the last glacial cycle's coldest temperature (LGM) and this glacial cycle's hottest temperature (HCO). In Greenland the Little Ice Age temperature nadir was invariably the coldest temperature after the HCO peak temperature (except Kobashi [64]). See the readme file (Figshare) for a detailed description of the methodology. Ice core data citations [64], [67]–[73].

S18 Figure. Sixteen polar ice core temperature plots delineating key glacial cycle landmark dates.

Annotated temperature plots from 16 polar ice cores spanning key glacial cycle landmark dates-temperatures, including the Last Glacial Maximum (LGM), Holocene Climate Optimum (HCO), Little Ice Age (LIA) temperature nadir, and the mid climate reference period mean (1961-1990 RPM) or its nearest proxy. For analytical-descriptive purposes the glacial cycle peak temperature closest to the end of the prolonged-steep interglacial temperature rise was termed the Holocene Climate Optimum (HCO); the lowest post-HCO temperature trough during the LIA period (mid-13th to mid-19th centuries) was termed the Little Ice Age temperature nadir. The lowest glacial cycle

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temperature trough reached at the end of the last glacial cycle immediately prior to the sustained interglacial temperature rise was termed the Last Glacial Maximum (LGM). The Holocene interglacial was the period between the LGM and HCO. The new ice age was the period after the HCO peak temperature and period. See the readme file (Figshare) for a detailed description of the methodology. Ice core data citations [64], [67]–[73].

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